Response to Letter Regarding Article, “Heart Failure, Saxagliptin and Diabetes Mellitus: Observations From the SAVOR-TIMI 53 Randomized Trial”

We thank Drs Muskiet, Tonneijck, and van Raalte for calling attention to the potentially detrimental consequences of simultaneous inhibition of dipeptidyl peptidase 4 and angiotensin-converting enzyme (ACE). They note correctly that in Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications (SAVOR-TIMI 53), more patients treated with ACE inhibitors at baseline were subsequently hospitalized for heart failure. However, this observation alone is likely a result of confounding by indication, because patients at highest risk of heart failure are more likely to be treated with this class of drug in the first place. A similar observation was seen with β-blockers.

Despite elegant physiological studies suggesting a potential hemodynamic interaction between dipeptidyl peptidase 4 inhibitors and ACE inhibitors, there were no differences in heart or blood pressure changes after randomization according to baseline ACE inhibitor use in patients treated with saxagliptin or placebo (all P for interaction >0.10). Nor were there any clinical consequences of baseline ACE inhibitor use on the primary end point of cardiovascular death, myocardial infarction, or ischemic stroke (baseline ACE inhibitor: saxagliptin, 7.3% versus placebo, 6.9%; HR, 1.08; 95% CI, 0.91–1.27; P = 0.39; or for interaction=0.23), the secondary end point, which included the primary end point plus hospitalization for unstable angina, heart failure, or coronary revascularization (baseline ACE inhibitor: saxagliptin, 12.9% versus placebo, 13.2%; HR, 0.95; 95% CI, 0.85–1.07; P = 0.41 in comparison with no baseline ACE inhibitor: saxagliptin, 12.7% versus placebo, 11.5%; HR, 1.11; 95% CI, 0.98–1.27; P = 0.11; or for interaction=0.08), or hospitalization for heart failure alone (baseline ACE inhibitor: saxagliptin, 3.6% versus placebo, 3.1%; HR, 1.19; 95% CI, 0.95–1.49; P = 0.14 in comparison with no baseline ACE inhibitor: saxagliptin, 3.3% versus placebo, 2.4%; HR, 1.39; 95% CI, 1.06–1.83; P = 0.02; or for interaction=0.38).

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Benjamin M. Scirica, MD, MPH
Eugene Braunwald, MD
TIMI Study Group
Cardiovascular Division
Brigham and Women’s Hospital
Boston, MA

Itamar Raz, MD
Diabetes Unit
Division of Internal Medicine
Hadassah Hebrew University Hospital
Jerusalem, Israel

Matthew A. Cavender, MD, MPH
David A. Morrow, MD, MPH
TIMI Study Group
Cardiovascular Division
Brigham and Women’s Hospital
Boston, MA

Petr Jarolim, MD, PhD
Department of Pathology
Brigham and Women’s Hospital
Boston, MA

Jacob A. Udell, MD, MPH
Cardiovascular Division
Women’s College Hospital and Toronto General Hospital
University of Toronto
Toronto, Canada

Ofri Mosenzon, MD
Diabetes Unit
Division of Internal Medicine
Hadassah Hebrew University Hospital
Jerusalem, Israel

KyungAh Im, PhD
Amarachi A. Umez-Eronini, MPH
TIMI Study Group
Cardiovascular Division
Brigham and Women’s Hospital
Boston, MA

Basil S. Lewis, MD
Cardiovascular Research Institute
Lady Davis Carmel Medical Center and Ruth and Bruce Rappaport School of Medicine Technion-IT
Haifa, Israel

Darren K. McGuire, MD, MHSc
Cardiovascular Medicine
Department of Internal Medicine
University of Texas Southwestern Medical Center
Dallas, TX

Jaime Davidson, MD, PhD
Division of Endocrinology
Department of Internal Medicine
University of Texas Southwestern Medical Center
Dallas, TX

Gabriel Steg, MD
Département Hospitalo-Universitaire FIRE
INSERM U-1148
Université Paris-Diderot
Hôpital Bichat, AP-HP
Paris, France

Deepak L. Bhatt, MD, MPH
TIMI Study Group
Cardiovascular Division
Brigham and Women’s Hospital
Boston, MA

NHLI Imperial College
ICMS, Royal Brompton Hospital
London, UK

References
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Benjamin M. Scirica, Eugene Braunwald, Itamar Raz, Matthew A. Cavender, David A. Morrow, Petr Jarolim, Jacob A. Udell, Ofri Mosenzon, KyungAh Im, Amarachi A. Umez-Eronini, Pia S. Pollack, Boaz Hirshberg, Robert Frederich, Basil S. Lewis, Darren K. McGuire, Jaime Davidson, Gabriel Steg and Deepak L. Bhatt

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